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Effect of Antiepileptic Drugs on Plasma Carnitine Level in Children with Idiopathic Epilepsy

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Abstract

Background: Prolonged antiepileptic drugs treatment can result in secondary carnitine deficiency. Clinical studies indicate a decrease in total and free plasma carnitine level in children treated with old antiepileptic drugs especially valproate.

Aim of Study: Was to evaluate the plasma carnitine level in children with idiopathic epilepsy treated with old antiepileptic drugs (valproate and carbamazepine) and new antiepileptic drugs (leviteracetam and oxcarbazepine).

Patients and Methods: This study was a prospective study including 50 patients with newly diagnosed idiopathic epilepsy classified into four groups according to their antiepileptic drug treatment into: Group 1, 20 patients received valproic acid. Group 2, 10 patients treated with carbamazepine. Group 3, 10 patients treated with leviteracetam. Group 4, 10 patients treated with oxcarbazepine. The study was carried out in duration of 1 year from January 2017 to January 2018.

Results: There was significant difference between mean plasma level of carnitine in children treated with valproate and the controls. There was inverse correlation between the duration of treatment with valproate and the mean plasma carnitine level. There was inverse correlation between the level of valproate and the mean plasma carnitine level. The higher the level of valproic acid, the more significant decrease in the mean plasma carnitine level.

Conclusion: Valproic acid was the only antiepileptic drug reported to cause carnitine deficiency. Also this study showed inverse correlation between plasma carnitine level and duration of treatment with valproic acid. The longer the duration of treatment, the more significant decrease in mean plasma carnitine level. Also, there was inverse correlation between the level of valproate and the mean plasma carnitine level. The higher the level of valproic acid, the more significant decrease in the mean plasma carnitine level.

Key Words: *Valproate – Carnitine deficiency – Antiepileptic drugs.*

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Introduction

PROLONGED antiepileptic drugs treatment can result in secondary carnitine deficiency. Clinical studies indicate a decrease in total and free plasma carnitine level in children treated with old antiepileptic drugs especially valproate [1].

Carnitine is a protein that is essential to the metabolism of long chain fatty acids that are metabolized in the mitochondria within the cell. Each molecule of fat has to be transported across the mitochondrial membrane by binding with a molecule of carnitine [2].

Carnitine deficiency is manifested as, encephalopathy; the patient may present limp, unresponsive and comatosed, myopathic presentation, the patient may have hypotonia or proximal muscle weakness. Cardiomyopathy has also been observed. Progressive cardiomyopathy usually manifests at an older age [3].

Patients and Methods

The study was carried out in Tanta University Hospital Pediatric Department, Neurology Unit. Fifty children with newly diagnosed idiopathic epilepsy selected from those attending the pediatric neurology outpatient clinic and enrolled in the study with patients classified into four groups according their antiepileptic drug treatment into: Group 1, 20 patients received valproic acid as momotherapy without any antiepileptic drug treatment before. Group 2, 10 patients treated with carbamazepine. Group 3, 10 patients treated with leviteracetam as monotherapy. Group 4, 10 patients treated with oxcarbazepine as monotherapy. Twenty healthy children served as control group with the

same age range. The study was carried out in duration of 1 year from January 2017 to January 2018.

Inclusion criteria:

1- All the epileptic children had no history of liver, renal or metabolic disease or history of AEDs or carnitine intake before the study.

2- These patients with idiopathic epilepsy had no apparent cause of epilepsy such as structural problem in the brain or metabolic disorder.

3- Positive family history of epilepsy in most of cases.

4- Patients with normal brain Magnetic Resonance Imaging (MRI) study.

5- Normal intelligence.

Exclusion criteria:

1- Patients with symptomatic epilepsy.

2- Patients with liver or renal diseases.

3- Patients with hypotonia or progressive weakness.

All patients were subjected to complete history taking, thorough physical examination, magnetic resonance imaging, electroencephalogram and estimation of plasma level of carnitine before the start of treatment and after 6 momths of antiepileptic drug intake.

Statistical analysis:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, paired *t*-test, linear correlation coefficient and Analysis of variance [ANOVA] tests by SPSS V 17.

1- $\text{Mean} = \frac{\Sigma\chi}{n}$

Where:

Σ = Sum.

n = Number of observations.

2- Standard Deviation [SD]:

$$SD = \sqrt{\frac{\Sigma | X - X^2}{n - 1}}$$

Paired t-test:

$$t = \frac{\bar{X}d}{\sqrt{\quad}}$$

Where:

$\bar{X}$ = Mean's difference between pre and post.

SEd = Standard error of the difference between pre and post.

Unpaired student *t*-test was used to compare between related sample.

Linear correlation coefficient [r]:

$$r = \frac{\Sigma (X - X)(y - \bar{y})}{\sqrt{\{\Sigma (X - X)2\}\ \{\Sigma (y - \bar{y})2\}}}$$

Where:

X = Independent variable.

Y = Dependent variable.

Linear correlation coefficient was used for detection of correlation between two quantitative variables in one group.

Analysis of variance [ANOVA] tests. According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data.

p-value >0.05 Non significant.
p-value ≤0.05 Significant.
p-value <0.01 Highly Significant.

Results

Table (1): Comparison between the mean plasma carnitine level in children with epilepsy and the control children after treatment.

Groups	Carnitine level (µmol/L)		ANOVA		Groups and controls
	Range	Mean ± SD	F	*p*-value	
Valproate	40-57	47.600±5.605	306.017	<0.001*	*p*1 <0.001*
Carbamazepine	82-90	87.200±2.936			*p*2 0.326
Leviteracetam	87-97	93.000±3.528			*p*3 0.853
Oxcarbazepine	82-95	89.400±4.600			*p*4 0.929
Controls	85-95	91.000±3.590			

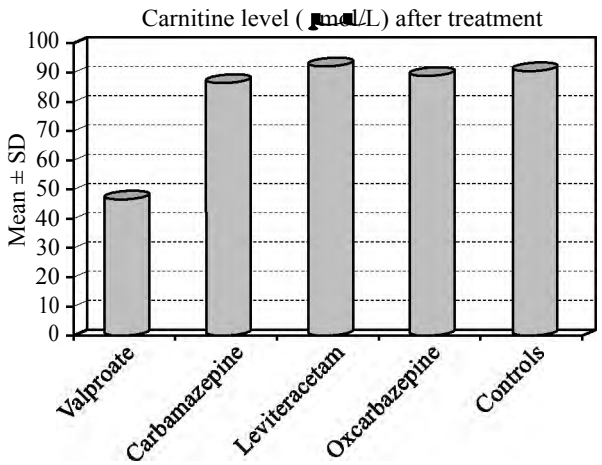

Fig. (1): Comparison between the mean plasma carnitine level in children with epilepsy and the control children after treatment.

Table (1) and Fig. (1) show that there was significant difference between mean plasma carnitine level in children treated with valproate after

receiving treatment and the controls but there was no significant difference between mean plasma carnitine level in children treated with carbamazepine, leviteracetam and oxcarbazepine after receiving treatment and the controls.

Table (2): Comparison of the mean serum level of plasma carnitine level in children treated with valproic acid before and after treatment.

Groups	Carnitine level (µmol/L)		*p*-value
	Before treatment	After treatment	
Valproate:			
Range	79-97	40-57	<0.001*
Mean ± SD	85.7±5.212	47.6±5.605	

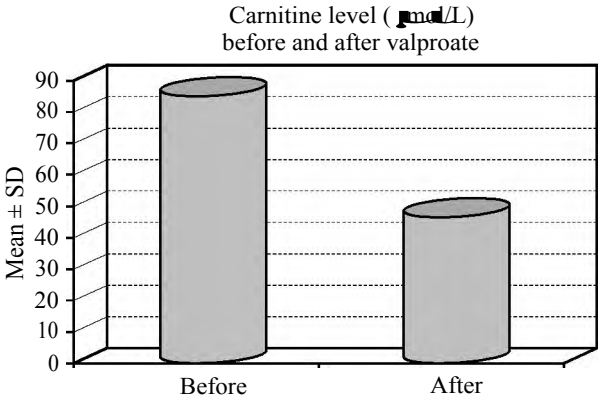

Fig. (2): Comparison of the mean serum level of plasma carnitine level in children treated with valproic acid before and after treatment.

Table (2) and Fig. (2) show that there was significant decrease in mean plasma carnitine level after treatment with valproate.

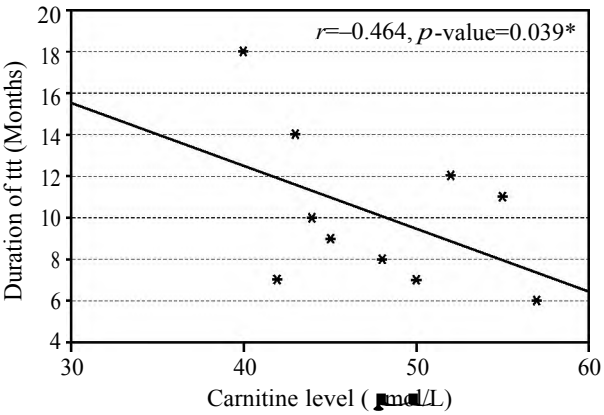

Fig. (3): Correlation between duration of treatment with valproate and carnitine level.

There was inverse correlation between the duration of treatment with valproate and the mean plasma carnitine level. The longer the duration of treatment, the more significant decrease in plasma carnitine level.

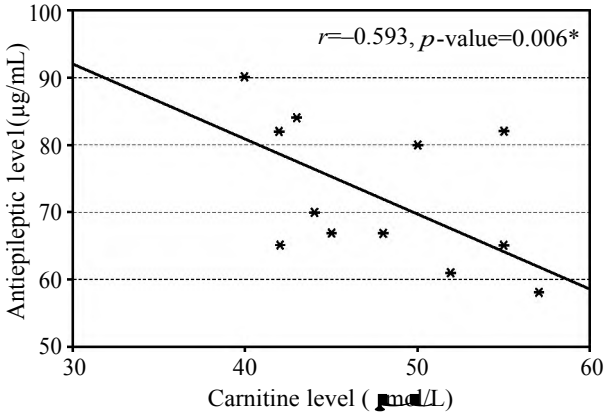

Fig. (4): Correlation between level of valproate and mean plasma carnitine level.

There was inverse correlation between the level of valproate and the mean plasma carnitine level. The higher the level of valproic acid, the more significant decrease in the mean plasma carnitine level.

Discussion

The results of this study agree with Qiliang et al., [4], who measured free carnitine and acylcarnitines levels in 299 children with epilepsy treated with valproate monotherapy between June 2014 and September 2015 were compared with age-and sex-matched 299 healthy controls. Results showed that children treated with valproate monotherapy had lower free carnitine levels than the controls.

Also, the results of this study agree with Nakamura et al., [5] who measured plasma total and free carnitine levels in four groups of children: Group (1) who treated with valproic acid as monotherapy (n=43), Group (2) who treated with valproic acid plus other antiepileptics as polytherapy (n=91), Group (3) who treated with other antiepileptic drugs alone (n=43), and Group (4) normal patients (n=89). The mean free carnitine level was significantly lower in both the valproic acid monotherapy and polytherapy groups compared with normal subjects. Comparison of valproic acid polytherapy and monotherapy yielded significantly lower free carnitine levels in the polytherapy group.

The results of this study also agree with Cansu et al., [6] who measured serum concentrations of total carnitine, free carnitine and acylcarnitine in 56 epileptic children, 28 treated with valproic acid (Group 1), 28 treated with oxcarbazepine (Group 2) and 28 treated with leviteracetam (Group 3) and 28 healthy controls (Group c). Duration of treatment was 6-12 months in Groups 1, 2 and 3. Results showed lower carnitine level in children treated with valproic acid than controls while no significant

difference in carnitine level between children treated with oxcarbazepine and controls.

The results of this study also agree with Murat et al., **[7]** who measured serum concentrations of total carnitine, free carnitine and acylcarnitine in 50 patients with epilepsy, 3 to 14 years of age, who were treated with valproate only for a mean of one year and free of abnormal neurologic findings or nutritional problems. The control group consisted of 30 healthy children. Results showed that children treated with valproate monotherapy had lower free carnitine levels than the controls.

The results of this study agree with Werner et al., **[8]** who measured serum carnitine longitudinally before and after therapy in 15 patients treated with valproic acid, 14 patients treated with carbamazepine and 20 healthy children. The patients who received valproic acid showed a significant reduction in free (and total) serum carnitine with valproic acid in comparion with controls. Such an effect was not found in patients treated with carbamazepine.

The results of this study also agree with Fung et al., **[9]** who measured serum concentrations of total carnitine, free carnitine and acylcarnitine in 43 children with epilepsy who were treated solely with valproate for a mean of 6 months. The control group consisted of 30 healthy children. Results showed that children treated with valproate monotherapy had lower free carnitine levels than the controls.

The results of this study agree with Semra kurel et al., **[10]** who studied serum concentrations of total and free carnitine in 20 healthy children, 20 children with epilepsy treated with oxcarbazepine monotherapy and 20 children with epilepsy who treated with carbamazepine as monotherapy. The assays were performed between 3 and 6 months of oxcarbazepine and carbamazepine treatment.

No significant difference was observed in the level of total and free carnitine levels between healthy group and epileptic chidren treated with carbamazepine and oxcarbazepine. Results suggest that neither oxcarbazepine nor carbamazepine as monotherapy causes carnitine deficiency in otherwise healthy children with primary idiopathic epilepsy.

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تأثير العلاج بالآدوية المضادة للصرع على مستوى مادة الكارنيتين بالبلازما فى الآطفال المصابين بالصرع غير معروف السبب

إن إستخدام آدوية علاج الصرع لفترة طويلة قد ينتج عنه نقص مادة الكارنيتين وقد وجد آن الدراسات الإكلينيكية تشير إلى نقص مادة الكارنيتين بنوعيها الحر والكلى فى الآطفال الذين تم علاجهم بآدوية علاج الصرع القديمة وخاصة مادة (صوديوم قالبرويت).

الهدف من الدراسة: تقييم مستوى مادة الكارنيتين بالبلازما فى الآطفال المصابين بالصرع غير معروف السبب والذين تم علاجهم بالآدوية المضادة للصرع.

طرق البحث: شملت هذه الدراسة خمسين طفل مصابين بالصرع مجهول السبب من كلا الجنسين من عمر عامين وحتى ١٥ عام وتم تقسيمهم إلى آربع مجموعات: المجموعة الآولى: ٢٠ طفل تم علاجهم بعقار (صوديوم فالبرويت) فقط. المجموعة الثانية: ١٠ آطفال تم علاجهم بعقار (الكاربامازيبين). المجموعة الثالثة: ١٠ آطفال تم علاجهم بعقار (الليفيتيراسيتام). المجموعة الرابعة: ١٠ آطفال تم علاجهم بعقار (الآوكسكاريازيبين). وتم إختيار عشرين طفلا آصحاء لإجراء المقارنة.

النتائج: قد آوضحت هذه الدراسة عدم وجود فرق إحصائى فى قيمة وسط مستوى مادة الكارنيتين قبل العلاج بالآدوية المضادة للصرع التى تتضمنتها الدراسة فى الآطفال المصابين بالصرع والآطفال الآصحاء. كما آوضحت وجود فرق إحصائى فى قيمة وسط مستوى مادة الكارنيتين قبل وبعد العلاج بعقار الصوديوم فالبرويت حيث قل مستوى الكارنيتين بعد العلاج، ولم يلاحظ هذا الفرق الإحصائى فى الآطفال الذين تم علاجهم بعقار الكاربامازيبين والليفيتيراسيتام والآوكسكاربازيبين. كما آظهرت الدراسة وجود علاقة عكسية بين مادة العلاج بعقار الصوديوم فالبرويت ومستوى مادة الكارنيتين، فكلما زادت مدة العلاج بالصوديوم فالبرويت كلما قل مستوى مادة الكارنيتين بالبلازما. كما آظهرت الدراسة وجود علاقة عكسية بين مستوى عقار الصوديوم فالبرويت بالدم ومستوى مادة الكارنيتين، فكلما زاد مستوى مادة صوديوم فالبرويت كلما قل مستوى مادة الكارنيتين بالبلازما.

الإستنتاج: عقار (الصوديوم فالبرويت) هو العلاج الوحيد المضاد للصرع الذى يسبب نقص مادة الكارنيتين بالبلازما.